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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,383	02/05/2002	Marco Thyes	0480-01211	2952

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EXAMINER	
OH, TAYLOR V	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/889,383	**Applicant(s)** THYES ET AL.	
	Examiner Taylor Victor Oh	**Art Unit** 1625	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 February 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 1-2.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see pages 2-7.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

It is noted that applicants have filed an Amendment after the Final Rejection on 2/17/05 ; applicants' attorney has addressed the issues of record. The proposed amendment will be entered ,but it is not a condition for allowance.

The Status of Claims

Claims 1-2 are pending.

Claims 1-2 have been rejected.

Claim Rejections-35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over Warner Lambert Pharmaceutical Co.(GB 1226318).

The rejection of Claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over Warner Lambert Pharmaceutical Co.(GB 1226318) is maintained for the reasons of the record on 5/26/04.

Applicants' attorney has not rebutted the claim rejections *1-2* under 35 USC 103 (a).

Applicants' Argument

2. Applicants argue the following issues:

1. Nothing in the teaching of GB 1,226,318 suggests or implies that the amount in which the carboxylic acid is employed has an influence on how much or how little of the undesired by-product ethyl 3-dimethylamino-2-phenylpropionate remains in the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate; furthermore, the teaching of GB 1,226,318 does not even suggest that the amount of the undesired propionate can be influenced by the disclosed process;

2. The claims are related to the equivalents of acid per total amount of the carboxylate (cis and tans isomers), whereas the prior art is related to the amount of trans-carboxylate present in the a mixture of trans-carboxylate and cis-carboxylate; the prior art' molar ratio of the acid to the mixture of trans-carboxylate and cis-carboxylate is 0.31 in the Ex. 1, whereas the claimed ratio is from 0.75 to 2.0; therefore, they are not overlapped;

3. According to the prior art , it serves no purpose when the acid amount goes beyond the range of 1.0 to 1.2 mol of acid per mol of trans-carboxylate ; likewise, a similar separation of trans-carboxylate and cis- carboxylate to be achieved by extending the time frame beyond its range of from 5 to 20 minutes serves no purpose ;

4. The results obtained from the applicants' process are unexpected results;

5. The teaching of the prior art has not established a prima facie case of obviousness.

The applicants' argument have been noted, but these arguments are not persuasive. First, with respect to the first argument, the Examiner has noted applicants' argument. However, regardless of the influential role of the carboxylic acid in the process, the issue is the reduction of impurities, such as ethyl 3-dimethylamino-2-phenylpropionate below 0.1 %. The prior art does teach that the content of ethyl 3-dimethylamino-2-phenylpropionate present in the final product (a trans form of ethyl 2 –dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) is less than 0.25 % in the mixture (see col. 4, lines 69-70), which means that it is overlapped with the claimed range below 0.1 %. Furthermore, MPEP (2144.05(R-1)) supports that there is no difference between the prior art and the current invention:

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.");< ** *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809

CCPA 1969. Therefore, the prior art process is still relevant to the claimed invention.

Second, with respect to the second argument, the Examiner has noted applicants' argument. However, the claimed ranges and the prior art ranges do not overlap but are close enough that one skilled artisan in the art would have expected them to be in the similar reaction condition in the absence of an unexpected result. MPEP (2144.05(R-1)) further presents the following discussion of the overlap or the not-overlap of the ranges :

> In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped.); *In re Geisler*, 116 F.3d 1465, 1469-71, 43 USPQ2d 1362, 1365-66 (Fed. Cir. 1997) (Claim reciting thickness of a protective layer as falling within a range of "50 to 100 Angstroms" considered *prima facie* obvious in view of prior art reference teaching that "for suitable protection, the thickness of the protective layer should be not less than about 10 nm [i.e., 100 Angstroms]." The court stated that "by stating that suitable protection' is provided if the protective layer is about' 100 Angstroms thick, [the prior art reference] directly teaches the use of a thickness within [applicant's] claimed range."). Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same

properties. Therefore, the prior art process is still relevant to the claimed invention.

Third, with respect to the third argument, the Examiner has noted applicants' argument. However, Warner Lambert Pharmaceutical Co reference does indicate that the reaction time can be in the range of from 5 to about 20 mins or a longer (see col. 2, lines 61-64), whereas the current invention is from 0.5 to 2 hours. The claimed ranges and the prior art ranges do not overlap but are close enough that one skilled artisan in the art would have expected them to be

in the similar reaction condition in the absence of an unexpected result. Furthermore, the limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Reaction time is well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity in a chemical process. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to modify the prior art reaction time to the claimed one by routine experimentation in order to control the selectivity of the desired product. This is because the skilled artisan in the art would expect such a modification to be successful and to be selective for the desired product.

Fourth, with respect to the fourth and fifth arguments, the Examiner has noted applicants' argument. However, attorney's arguments of unexpected results can not take the place of evidence in the record; furthermore, on the contrary to applicants' argument, Warner Lambert Pharmaceutical Co does disclose the process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate to a less than 0.25 % in the mixture (see col. 4, lines 69-70) containing ethyl 2 –dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate; furthermore, it is well-known that the ethyl 2 –dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate compound has possessed the therapeutic activity as analgesics. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to reduce its content of impurity further to a less than 0.1 % for purpose of using the desired final product as a safe analgesic drug. This is because the

skilled artisan in the art would expect the purest compound to be the safest drug suitable for the therapeutics.

Therefore, the Examiner maintains the rejection of all the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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3/15/05

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